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<b>(54) Title:</b> COMPOSITION FOR THE TREATMENT OF IMPAIRED HAIR GROWTH  <b>(57) Abstract</b>  A composition for the treatment of alopecia, characterized in that it contains an effective concentration of at least one anti-alopecia acting gibberellin. A method for treating and preventing alopecia utilizing the composition is also disclosed.		

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**COMPOSITION FOR THE TREATMENT OF IMPAIRED HAIR GROWTH**

**Technical field, background and problem to be solved.**

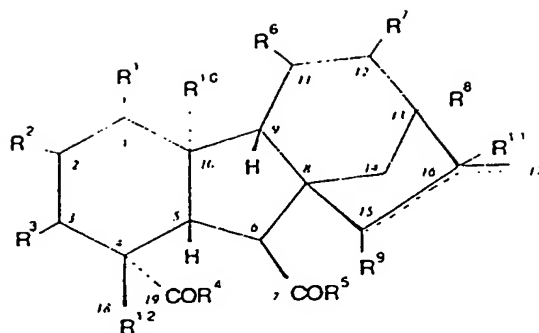
The present invention relates to a composition that  
5 contains gibberellins, and the use of such compositions for  
the treatment of impaired hair growth (alopecia), such as  
androgenic alopecia in mammals (including humans) and  
preferably for the treatment of male pattern baldness. The  
inventive concept is adapted for the treatment method of  
10 progressive (on-going) alopecia that is reversible and  
therefore can be cured. This method enables that the final  
state of alopecia may be delayed.

The hair can be divided into different types - hair of  
the scalp and hair of the remaining parts of the body, e.g.  
15 eye-brow, beard and fine vellus hair. The invention is  
primarily directed towards the treatment of alopecia of the  
scalp.

Alopecia means decreased hair growth on the scalp and  
results in more or less apparent baldness. It may be  
20 divided into two main groups - diffuse and patchy. The most  
common type of alopecia in men is male pattern baldness or  
androgenic alopecia (diffuse). This type of loss of scalp  
hair is androgen-dependent and increases with age. The  
triggering factor has been considered to be purely  
25 genetical. Other factors giving rise to alopecia are: fever  
and stress; syphilis; endocrine causes; nutritional;  
certain drugs; hair shaft defects etc.

The gibberellins (GAs) are a group of compounds which are  
found in higher plants and in certain fungi. Their basic  
30 carbon skeleton is (Formula I):

**CONFIRMATION  
COPY**



10 The meanings of the groups  $R^1$  to  $R^{10}$  are the same as  
 given in WO 9108751 (US S.N. 07/854,615 being its US  
 counterpart) which hereby is incorporated by reference.  
 Naturally occurring GAS may have alcoholic hydroxy groups  
 directly attached to any of the positions 1, 2, 3, 10, 11,  
 12, 13, 15 and 16. A carboxy group (possibly lactonized,  
 15 see below) is always present at positions 4 and 6. An extra  
 carboxy group may be present at positions 4 (gives geminal  
 carboxies) and 10. These hydroxy and carboxy groups may be  
 in the form of a glycosidic ether or ester, respectively,  
 20 or, if the geometric configuration so permits, in the form  
 of a lactone (e.g. between a hydroxy at position 10 and a  
 carboxy at position 4). When present the glycosidic bond to  
 a gibberellin is normally of the O- $\beta$ -type with the sugar  
 moiety selected from D-glucose, D-galactose, D-arabinose  
 25 and D-xylose. In nature the gibberellins with the highest  
 activity are derived from basic compounds exhibiting the  
 gibberellin skeleton (formula I). In plants the biological  
 (hormonal) activity is increased by the oxidation of a  
 methyl group ( $\text{CH}_3$ -) at position 10 to a hydroxy methyl  
 30 group ( $\text{HOCH}_2$ -) or to an aldehyde group ( $\text{OCH}$ -), or simply by  
 direct hydroxylation at the 10-carbon (gives 10-OH  
 gibberellins). In case the 10-carbon is hydroxylated,  
 lactonization can occur subsequently with a carboxy at  
 position 4 resulting in a 4-10 lactone bridge (essential  
 35 for high activity in non-animal species (plants, fungi  
 etc). Other transformations that increase the activity in  
 non-animal species are 3- and 12-hydroxylations (resulting

in 3-OH and 12-OH gibberellins), possibly combined with the oxidations and lactonizations previously mentioned.

The active GAs regulate growth and differentiation of non-animal species, such as plants and fungi. They are  
5 active in very small amounts. Their mode of action is through receptor binding and transcripter initiation, i.e. analogous to the steroid hormones in mammals. The normal amounts of GAs in plant material are in the range of 10-100 ng per g fresh weight. The concentration in pollen is about  
10 one order of magnitude higher than in vegetative tissue, i.e. up to µgs per gram.

Only once it has earlier been suggested to incorporate gibberellins (EP 79,074) in a hair composition with a proposed activity against alopecia. Five particular  
15 gibberellins were then mentioned - (i) four with a lactone bridge between positions 2 and 5 (designated GA<sub>1</sub>, GA<sub>2</sub>, GA<sub>3</sub>, and GA<sub>4</sub>), and (ii) one (designated GA<sub>3</sub>) with a lactone bridge between positions 10 and 4 together with a methylene group (CH<sub>2</sub>-) at position 4 binding to an unspecified group.  
20 The doses suggested were relatively high and no connection was made to the cause of the alopecia to be treated. In the corresponding US patent (4,508,707), activity against alopecia is not suggested, instead the composition is focused on various hair tonic effects, such as promotion of  
25 hair care and the prevention of dandruff and itch. In Derwent abstract 83-47910K/20 (Japanese patent application 81159277) the same applicant states that the same GAs imperatively are combined with a protease in a hair care composition.

30 It ought to be mentioned that the designations GA<sub>1</sub>, GA<sub>2</sub>, GA<sub>3</sub>, and GA<sub>4</sub> in EP 79,074, US 4,508,707 and Derwent Abstract 83-47910K/20 are misleading because they are not according to accepted practice. Further on in this specification all designations are according to accepted  
35 nomenclature.

Compositions containing pollen or pollen components have repeatedly been suggested in connection with improving hair appearance.

Other compositions with an alleged effect on i.a. alopecia have previously been presented in: FR 2,641,164 that describes a dietetic composition containing 1-30% pollen; and Derwent Abstracts Nos 89-194760-3/27 and No 89-214776/30 that give various compositions containing water extracts of pollen. A recent composition based on hop, particularly phytohormones present in hop pollen, has been suggested for androgen-dependent alopecia (DE 4,121,544, Derwent Abstract No 93-009623/02).

10 Hair lotions containing pollen preparations but without reference to alopecia are described in Derwent Abstracts Nos 91-337523/46 (alcoholic pollen extract), 83-843474/50 (ethanolic pollen extract) and 77-64145Y/36 (intact pollen).

15 DE 3,912,637 (Derwent Abstract No 91007926/02) describes a composition intended for the treatment of hair losses due to hormonal deficiency. The composition contains as active components ginseng and Royal Jelly.

20 Various therapeutic uses of GAs have been thoroughly discussed in WO 9108751 (Odén P).

FR 2,587,208 suggests a composition for the treatment of diffuse alopecia that is androgen dependent. The constituents of the composition are alleged to act synergistically. One of the constituents may be zinc-ions.

25 The above-mentioned publications are illustrative that during the centuries and depending on geographical area there have been great demands for agents that act against alopecia in both male and females. In spite of this and the very many compositions that have been suggested, the common idea among doctors has been that "Patent remedies and hair  
30 tonics are of no proven value, and patients should be told of this" (MacKee, R.M., Clinical Dermatology, Oxford Medical Publications (1986) p. 192).

35 It has now been realized that, in particular androgenic alopecia, is under strong influence of factors other than genetical, and that it is possible to inhibit or at least delay its onset. Nutritional factors and stress factors

that decrease the supply of nutrients to the hair follicles enhance the negative effects of androgens on hair growth. I have now realized that gibberellins, in spite of the earlier loss of success with them, may be extremely  
5 valuable, if they are administered to the scalp in a anti-androgenic effective amount.

The action of the active gibberellins are, based on today's knowledge, that they bind to the androgen receptor thereby blocking binding of androgens and inhibiting the  
10 negative effect the androgen-receptor complex has on hair development.

#### The invention

The composition of the invention is characterized by  
15 containing an effective concentration or amount of one or more gibberellins with activity against androgenic alopecia. By the term "effective concentration/amount" is meant a concentration/amount that delays or prevents this type of alopecia, i.e. with respect to androgenic alopecia  
20 the concentration/amount is anti-androgenic. The exact concentration/amount depends on the specific gibberellin(s) selected and other ingredients of the composition, but as a rule of thumb the total level of GAs are often lower than in the gibberellin compositions presented in the prior art  
25 (EP-A-79,074). Based on present knowledge it is believed that the preferred concentration is in the range  $10^{-9}$ - $10^{-6}$  g per gram of the final composition that is to be applied directly onto the scalp. For gibberellins with low  
30 biological activity, for instance those having no hydroxyl group at any of positions 3, 12 and 13 or no lactone bridge, the upper and lower limits of the interval may have to be multiplied with a factor  $10^3$  or  $10^4$ . The four gibberellins described in EP-A-79,074 (having a 2-5 lactone bridge) are likely to be such low-activity gibberellins.

35 Preferred gibberellins are illustrated by those having (i) a lactone bridge between positions 4 and 10 (as defined above) together with a hydrogen, methyl, hydroxymethyl or carboxy at position 4, optionally in combination with a

hydroxy at position 13, and/or (ii) a hydrogen or preferably a hydroxy group at at least one position selected from positions 3, 12 and 13. Examples of forms of gibberellins preferred at the priority date are GA<sub>1</sub> (= 3-β-HO-GA<sub>20</sub>) and GA<sub>20</sub>. Preferred GA-variants also encompass gibberellins in which the previously mentioned carboxy and/or hydroxy groups forms glycoside esters and ethers, respectively. GAs having a carboxy group (COOH) are particularly preferred because this group imposes a ionophoric property onto the molecule enabling the formation of hydrophobic ion complexes, the absorption of which may be enhanced according to general principles known in the field. Other advantageous forms of GAs carry a labilely esterified carboxy group that may become hydrolysed during use.

General guidance if a certain GA may be useful in the invention can be obtained by testing for hormonal/biological activity in non-animal species. A suitable model is the Tan-ginbozu dwarf rice drop bioassay (Murakami, Botan. Magazine (Tokyo) 81 (1968) p. 33-). However, final judgement of specific anti-androgenic effects against alopecia requires verification by case studies, for instance as described in the experimental section below.

Several different GAs are of fungal origin and are commercially available in bulk quantities. Other GAs can be synthesized from fungal GAs or obtained from other sources, such as higher plants, in particular from pollen.

In connection with the present invention it has been realized that the plant gibberellins belong to the GAs that are extremely potent regarding stopping progressive alopecia. 3-β-OH-GA<sub>20</sub> (= GA<sub>1</sub>) and GA<sub>20</sub> and corresponding glycoside esters and glycoside ethers, for instance, are found in pollen.

Due to the very low amounts needed for an effect on alopecia, the inventive compositions do not require highly purified forms of GAs. It suffices to use partly purified fungal or more preferably partly purified plant and pollen preparations that are enriched in GAs (preferably in the



form of extracts). Pollen grains as such have been suggested to be incorporated into various cosmetic preparation. However, with respect to the availability of GAs, pollen grains are not recommendable to use in this invention because the pollen envelope will effectively prevent the release of their content of GAs.

Thus in case of preparations containing gibberellins derived from pollen, the pollen envelope must have been disintegrated or the gibberellins otherwise released from the pollen interior. One way of doing this is by extraction with a solvent that dissolves the GAs of interest. Suitable solvents are pure organic solvents or solvent mixtures containing water and one or more water-miscible organic solvent, such as methanol, ethanol, acetone etc, optionally together with a water-immiscible solvent that is miscible with the above-mentioned mixture of water and a water-miscible solvent. The water content of the extracting solvent may in most cases vary between 0-25% (v/v), in particular between 2-25% (v/v). In case all components of the extracting solvent are physiologically acceptable the extract as such can be incorporated into the inventive compositions, otherwise the solvent has to be removed, for instance, by lyophilization, spray drying or evaporation under reduced pressure. Suitable extracting procedures gives extracts that are poor in protein components. Since pollen allergenicity is derived from proteins, it may be advantageous to secure complete removal of protein components (e.g. with Mw above  $2 \times 10^3$  dalton) by subjecting the extract to gel filtration or ultrafiltration. The extraction of GAs from plant material (including pollen) has been presented in WO 9108751 (Odén P).

In addition to GAs, the inventive composition may also contain minerals (compounds containing metal ions), vitamins and hair/skin nutrients. Vascular dilation agents have previously been recognized to have a positive influence on hair condition probably because they increase the blood flow to the richly vascular papilla. This latter type of agents may be included as well.

Minerals have a dual action in the inventive composition. Firstly, metal ions may form hydrophobic complexes with the carboxy forms of GAs thereby facilitating GA transport across the cell membranes. Secondly, they often act as essential micro nutrients (trace elements) and constituents in biological systems. In particular zinc has important functions in the growth of cells in the skin (cf. that deficiency in zinc in some cases may cause alopecia (hypozincaemia).  $\text{Zn}^{2+}$ -salts are particularly preferred to incorporate into the inventive compositions, e.g. zinc oxide ( $\text{ZnO}$ ), zinc chloride ( $\text{ZnCl}_2$ ) or zinc sulphate ( $\text{ZnSO}_4$ ). Preferably the zinc mineral is insoluble in aqueous media or in the composition. As an alternative, physiologically acceptable organic zinc compounds can potentially be used. The  $\text{Zn}^{2+}$ -concentration in the composition is often in the range 0-200 mM, most preferably 2-100 mM. The same ranges also apply for the metal ion in other micro nutrients (trace elements), although with variations in optimal subranges.

Vitamin E (= (+)- $\alpha$ -tocopherol) and vitamin H (= d-biotin) are recognized to be essential for normal hair growth and may be present in the inventive composition. The concentration range for vitamin E is in the normal case 0-100 mM, particularly 0.5-20 mM, and for vitamin H 0.01-50 mM, particularly 0.05-10 mM. A synergistic effect between vitamin E and GAs can not be excluded.

Vascular dilation agent that are useful in the invention shall be administratable topically onto the scalp to cause a local effect in the blood vessels of the scalp. The agent may be purely synthetic but in the field of hair conditioning it has been popular to use volatiles (particularly terpenes) that may be obtained from different plants, for instance oils from *Melaleuca alterniflora* Cheel that contains the volatile vascular dilation agents terpinen-4-ol (20-50%) and cineole (1-8%). The content of the vascular dilation agent in the final composition may be 0-10%, for instance 0.01-10%, with the particular choice of

plant volatiles, e.g. Melaleuca-derived volatiles in the range of 0.05-1%.

In addition to the above-mentioned hair growth active ingredients, the composition may also contain common liquid vehicles, for instance physiologically acceptable solvents, such as water, ethanol, glycerol etc; common ointment bases such as lipids; gel forming agents, such as polyalkylene glycols including polyethylene and polypropylene glycols; cellulose derivatives, etc.

In order to stabilize the composition it may also contain additives such as antioxidants; preservatives such as germicides; and detergents. Detergents may have a dual action by stabilizing the composition (in case it is an emulsion) and solubilizing lipid material around the hair root.

The inventive composition may be manufactured according to the commonly accepted principles for this type of hair compositions except that an active amount/concentration of the above-mentioned gibberellins is incorporated therein.

Thus the present composition may be in the form of an ointment, solution, gel etc.

The treatment protocol encompasses applying topically 1-5 times, preferably once or twice, each day, in an evenly spread layer, to a skin area suffering from alopecia, preferably human scalp, an effective amount of the above-defined gibberellins. The preferred dose of GAs is  $10^{-11}$  -  $10^{-6}$  g/cm<sup>2</sup> treated area. For the normal person suffering from alopecia this means that 0.5-10 ml of the inventive composition is given at each administration occasion, i.e.  $0.5 \times 10^{-9}$  -  $10^{-5}$  g active gibberellins. The scalp should be massaged when the composition has been applied. A previously applied composition should be removed at least prior to the first application of a day. For individuals in which the alopecia returns when the treatment is interrupted, years of treatment may be advisable. Preferably at about every fourth week, the treatment should be interrupted for a one-week pause.

It should be borne in mind that the treatment, like any previously known non-surgery protocol for treating alopecia, is only applicable to scalps where the hair follicles still are alive. Hair follicles may die, and  
5 since new follicles can not be formed in adults this will result in hair loss that is always irreversible.

EXPERIMENTAL PARTCOMPOSITION**Ingredients:**

- 5 Zinc oxide (ZnO) derma p.a., 0,025 M (0.2% in the final solution)
- (+)- $\alpha$ -Tocopherol, purity 67%, 0.0075 M (0.5% in the final solution)
- Ethanol, 95% (75% in the final solution)
- 10 Zinc chloride (ZnCl<sub>2</sub>), p.a., 0.02 M (0.25% in the final solution)
- Distilled water
- Standardized rye pollen extract containing 3  $\mu$ g/ml GA<sub>19</sub>,  
1  $\mu$ g/ml GA<sub>20</sub>, 2  $\mu$ g/ml GA<sub>53</sub> and 0.1  $\mu$ g/ml 3- $\beta$ -OH  
GA<sub>20</sub>. These GAs were present in the extract in both  
15 glycosidic ester forms and as free carboxy forms.  
The extract had been obtained by extracting rye  
pollen with a solvent for the gibberellins as  
described in WO-9108751 (Odén P) which hereby is  
incorporated by reference. Suitable solvents are  
20 methanol or ethanol, in both cases mixed with water  
(20% H<sub>2</sub>O). The extract (including the solvent)  
amounted to 3% in the final solution.

**Method of manufacture:**

- Basic batch: (+)- $\alpha$ -Tocopherol (purity 67%, 500 g) was mixed  
25 in a first container with zinc oxide (ZnO) derm. p.a. to a  
homogeneous viscous mass under nitrogen atmosphere (other  
inert gaseous media could also be used). The mixture was  
then "dissolved" in a total volume of 80 l ethanol (95%).  
The zinc oxide will appear as precipitate. Zinc chloride  
30 (ZnCl<sub>2</sub>, 250 g) was added to 20 l distilled water (pH  
adjusted to 4.0 with HCl) in a second container. The pH-  
value can be adjusted afterwards with NaOH in order to  
achieve a value suitable for preparation of a gel from the  
solution. The content of the second container was  
35 thereafter very slowly added under nitrogen atmosphere to  
the content of the first container. Finally, 3 kg of the  
standardized rye-pollen extract was added which relatively  
rapidly become dissolved in the mixture.

Basic batch with further ingredients: In a separate batch our basic batch was modified by incorporating biotin and an antioxidantia (Pyrogallin™ P, Nipa Biosides) into the ethanol solution prepared in the first container and lemon  
5 aroma essence, Aloe vera extract (concentrate 1:20 which gives 1% in the final solution), emulgator (0.5% in the final solution, Cremophor™ RH 410, BASF (Germany)).

Gel composition: Different combinations (A-C) were premixed separately.

- 10 A. (+)-tocopherol (5.20 g), Zinc oxide (2.08 g), Tea tree oil (2.08 g, Pioneer, Australia) and Tween™ 80 were mixed to a homogeneous suspension.  
B. Zinc chloride p.a. (2.73 g), distilled water pH 4.0 (218.56 g), Aloe vera concentrate 40:1 (5.46 g) and ethanol  
15 pollen extract (32.79 g) were mixed to a clear solution.  
C. Biotin (0.1 g), Progallin™ P (0.11 g), ethanol 95% (705.65 g) and Ciric aroma (5.46 g) were mixed to a clear solution.

Solution B was then mixed into solution C whereafter the  
20 mixture was added to suspension A. Klucel HF (9.37 g, Hercules Inc) was added slowly under vigorous agitation that was continued for several hours (optimally 2 hours). All operations, including premixing steps, were carried out under nitrogen atmosphere.

25

#### OPEN STUDY

Patients and Methods: Three men, aged 46 to 60, two from the North and one from the South of Sweden, with different scalp baldness where chosen as representative for the  
30 study. Two of the patients had genetical factors, father and grand father with a bald. Patient No. 2 had the common type of hair loss, the male pattern baldness.

Test person No.	Age(years)	Baldness
35 1	46	Temporal bald
2	52	Temporal bald
3	60	Middle of scalp

The study was carried out with the basic composition described above during a period of four months, because follicles of the terminal hair have cyclic growth pattern that can be divided into three parts, anagen or growing phase, catagen or resting phase, and telogen or shedding phase. Photos were taken before and after the test period. The treatment was carried out by applying 1-2 ml of the composition twice a day in periods of three weeks followed by a pause of one week before restarting the treatment cycle. The exact dosage was dependent on the area to be treated. The composition was applied in the morning after washing the hair and scalp with a mild shampoo. The solution was massaged on bald parts to enhance penetration. A second application was done before bedtime without removing the previous application. This means that in principle the application time was around 24 hours.

**Results:** The first results could be noted after two months. Fine hair, like vellus hair, began to grow on test persons No. 1 and 2. Test person No.3 with the bald in the middle of his scalp also got some thick hairs among the fine ones. After four months a difference in the hair growth could be observed. Test persons No.1 and 2, the men with the temporal balds, had signs of growth of hair on the outer parts of the bald which continued forward to the point that was the natural edge of the scalp before hair loss. On test person No.3, the new hair growth started in the middle of the bald.

P A T E N T   C L A I M S

1. A composition for the treatment of alopecia,  
characterized in that it contains an effective  
5 concentration/amount of at least one anti-alopecia  
acting gibberellin.
2. A composition for the treatment of alopecia according to  
claim 1, characterized in that the concentration of said  
10 at least one gibberellin is  $10^{-9}$  -  $10^{-6}$  g per g of the  
total composition.
3. The composition according to anyone of claims 1-2 for  
the treatment of alopecia, characterized in that at  
15 least one, preferably all of, said at least one  
gibberellin is present in pollen.
4. The composition for the treatment of alopecia according  
to anyone of claims 1-3, characterized in that at least  
20 one, preferably all of, said at least one gibberellin is  
present in rye pollen.
5. The composition for the treatment of alopecia according  
to anyone of claims 1-4, characterized in that at least  
25 one of said at least one gibberellin  
(i) has a lactone bridge between positions 4 and 10  
together with a hydrogen, methyl, hydroxymethyl or  
carboxy at position 4, optionally in combination with a  
13-OH group and/or a 3-OH group, and/or  
30 (ii) has a hydrogen or a hydroxy group at position 12,  
said gibberellins being optionally esterified or  
etherified at at least one of their hydroxy groups,  
preferably 12-OH or 13-OH, and/or at at least one of  
their carboxy groups, preferably at 6-carboxy.  
35
6. The composition for the treatment of alopecia according  
to anyone of claims 1-5, characterized in that at least  
one of said at least one gibberellin is GA<sub>20</sub> or 3- $\beta$ -OH



GA<sub>20</sub>, optionally being etherified or esterified at at least one of their hydroxy groups, preferably 12-OH or 13-OH, and/or at at least one of their carboxy groups, preferably at 6-carboxy, respectively.

5

7. The composition for the treatment of alopecia according to anyone of claims 1-6, characterized in that at least one of said at least one gibberellin is etherified or esterified, preferably via an O-β- bond to a  
10 carbohydrate selected from D-glucose, D-galactose, D-arabinose and D-Xylose.

15

8. The composition according to anyone of claims 1-7 for the treatment of alopecia, characterized in that at least one of said at least one gibberellin has been incorporated into the composition in the form of a pollen extract, either in dried form or in the form of the liquid extract, which extract has been obtained by extracting with a gibberellin-dissolving solvent.

20

9. The composition for the treatment of alopecia according to claim 8, characterized in that the extracting solvent is aqueous and contains a mixture of ethanol-water where water constitutes around 4-25 % (v/v).

25

10. The composition for the treatment of alopecia according to anyone of claims 1-9, characterized in that the composition contains mineral micro nutrients (trace elements), preferably providing a metal ion  
30 concentration within the range of 0-200 mM, such as 2-100 mM, based on the total composition.

35

11. The composition for the treatment of alopecia according to claim 10, characterized in that the metal ion is Zn<sup>2+</sup> and the mineral nutrient is zinc chloride and/or zinc sulphate and/or zinc oxide and/or other Zn-compounds that are physiologically acceptable when incorporated into the composition.

12. The composition for the treatment of alopecia  
according to anyone of claims 1-11, characterized in  
that the composition is in the form of a gel, a solution  
5 or an ointment.
13. A method for preventing alopecia in humans, preferably  
androgen dependent alopecia, characterized in that the  
composition according to anyone of claims 1-12 is  
10 applied to a human scalp suffering from alopecia.
14. The method according to claim 13, characterized in  
that the composition is applied 1-5 times each day for a  
prolonged period of months, preferably intermittent by  
15 an one-week pause every fourth week.
15. The method according to anyone of claims 13-14,  
characterized in that 0.5-10 ml of the composition is  
applied at each application occasion.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00423

## A. CLASSIFICATION OF SUBJECT MATTER

IPC : A61K 7/06, A61K 35/78, A61K 31/70

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC : A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BIOSIS, MEDLINE, CA SEARCH, WPIL, CLAIMS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A2, 0079074 (AYUKAWA TAIZO ET AL), 18 May 1983 (18.05.83) --	1-15
X	WO, A1, 9108751 (ODÉN, PER), 27 June 1991 (27.06.91) --	1-12
X	DE, A1, 4121544 (BRÜNEN, FRIEDRICH STEPHAN), 7 January 1993 (07.01.93) --	1-15
X	Derwent's abstract, No 83-843474/50, week 8350, ABSTRACT OF SU, 997681 (ALYE PARUSA PERFUME), 23 February 1983 (23.02.83) --	1-15

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

10 August 1994

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00423

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	Chemical Abstracts, Volume 111, No 6, 7 August 1989 (07.08.89), (Columbus, Ohio, USA), page 368, THE ABSTRACT No 45046w, ES, A, 2002589, (Valdes Diaz) 16 August 1988 (16.08.88) --	1-15
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Information on patent family members

02/07/94

International application No.  
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			EP-A-	0504254	23/09/92
DE-A1-	4121544	07/01/93	NONE		
ES-A-	2002589	16/08/88	NONE		
FR-A1-	2587208	20/03/87	NONE		